DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/07/2011 has been entered.

2. Claims 1-22, 35, 37-39, 66-85 are pending.

3. Claims 16 and 18-22 stand withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 07/09/2008.

4. Claims 1-15, 17, 35, 37-39 and 66-85 are currently pending and under consideration as they read on the recombinant mutant Der p 2 allergen of SEQ ID NO:36.

5. Applicant's IDS document filed on 11/07/2011 is acknowledged. Items that have been crossed off are not publications with publication dates, though they have been considered.

Double Patenting

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection

is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. Claims 1-15, 17, 35, 37-39 and 66-85 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 36-96 of copending Application No. 10/719,553. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims arrive at similar allergenic variants, and by what appears to the Examiner by the same method of selection, or if not by an obvious variant thereof. Specifically, Claims 36-96 teach a mutant Bet V 1 allergen with 1 or more substitutions, wherein said substitutions occur at many amino acid residues that are identical between the '553 application and the instant application, such as those recited in copending claim 37 and instant claim 22.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant's arguments filed on 11/07/2011 have been fully considered, but are not found persuasive.

Applicant argues:

> "Claims 1-15, 35, 37-39 and 66-85 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting over certain claims of co-pending application no. 10/719,553 ("the '553 application"). Applicants confirm that the '553 application has not issued as a patent. Accordingly, it is requested that the instant rejection be held in abeyance."

It is the Examiner's position that the rejection stands until the rejected claims are cancelled or until a terminal disclaimer is filed. In addition, this is not the last remaining rejection. Accordingly, the rejection is maintained.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-15, 17, 35, 37-39 and 66-85 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The limitation of being a 'mutant allergen of a naturally occurring allergen' is unclear because it is impossible to distinguish between a mutant and a naturally occurring sequence until such a naturally occurring sequence becomes part of the art in the field.

The limitation of "known homologous protein" is also unclear.

The scope of the claims would be changeable as more wild-type allergen sequences are identified.

The specification discloses on page 31, line 25 to page 32, line 2 a list of positions that can be mutated. However, this lists many positions and many particular amino acid substitutions at the specified positions that are present in homologous species. As such, would naturally occurring sequences with these mutations be considered mutants of naturally occurring species?

Correction is required.

Applicant's arguments filed on 11/07/2011 have been fully considered, but are not found persuasive.

Applicant argues:

> "The standard for definiteness is whether "those skilled in the art would understand what is claimed when the claim is read in light of the specification." *Orthokinetics, Inc., v. Safety Travel Chairs, Inc.,* 806 F.2d 1565, 1576 (Fed. Cir. 1986). Here, the Examiner has failed to provide a supportable basis for concluding that one of ordinary skill in the art would not understand what is claimed when the claims are read in light of the specification. It is noted at the outset that the claims call for a "recombinant mutant allergen of a naturally occurring allergen." The meaning of "naturally occurring allergen" is self-evident, i.e., an allergen that is obtained from the wild. A recombinant mutant allergen of a naturally occurring allergen is therefore simply a naturally-occurring allergen that has been mutated. Contrary to the Examiner's position, the phrase "recombinant mutant allergen of a naturally occurring allergen" is clear on its face. The phrase "known homologous protein" is similarly clear on its face. Additionally, the Examiner's position concerning the possibility that the scope of the claims may change as more wild-type allergen are identified is not believed to be well taken. Compliance with section 112 is measured against the knowledge of skill in the art at the time the application was filed. The possible discovery of additional wild-type allergens thus does not make the claims indefinite.
>
> Lastly, the response to the Examiner's query concerning whether "naturally occurring sequences" comprising particular amino acids at positions listed on page 31, line 25 to page 32, line 2 of the specification is straight forward. Naturally occurring allergens are not encompassed by the instant claims."

The meaning of "naturally occurring allergen" is self-evident, i.e., an allergen that is obtained from the wild. A recombinant mutant allergen of a naturally occurring allergen is therefore simply a naturally-occurring allergen that has been mutated. Contrary to the Examiner's position, the phrase "recombinant mutant allergen of a naturally occurring allergen" is clear on its face. The phrase "known homologous protein" is similarly clear on its face. Additionally, the Examiner's position concerning the possibility that the scope of the claims may change as more wild-type allergen are identified is not believed to be well taken. Compliance with section 112 is measured against the knowledge of skill in the art at the time the

> application was filed. The possible discovery of additional wild-type allergens thus does not make the claims indefinite.
>
> Lastly, the response to the Examiner's query concerning whether "naturally occurring sequences" comprising particular amino acids at positions listed on page 31, line 25 to page 32, line 2 of the specification is straight forward. Naturally occurring allergens are not encompassed by the instant claims."

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention in order to determine the metes and bounds of the claims. The meaning of the claim terms will be determined long after an application is filed and a patent is issued when relating to issues of infringement. It is the Examiner's job to make sure that when a patent issues the metes and bounds of the claims are clear so that one can determine whether or not there is infringement of a claim.

In the instant case, one of ordinary skill in the art at the time of filing would have known that the terms "known homologous protein" and "mutant allergen of a naturally occurring allergen" would change in meaning over time as new naturally occurring allergens and homologous proteins are discovered. So, at the time of filing, one of ordinary skill in the art would have known that the metes and bounds of the claims are unclear and indefinite.

As such, the rejection is maintained.

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 1-15, 17, 35, 37-39, 64 and 66-85 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a

way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is not in possession of:

A recombinant mutant allergen of a naturally occurring allergen, said naturally occurring allergen selected from the group consisting of Fagales group 1 allergens, Vespidae antigen 5 allergen$_s$, house dust mite group 1 allergens, house dust mite group 2 allergens and grass group 5 allergens and comprising wherein at least four mutations, which each reduce the specific IgE binding capability of the mutated allergen as compared to the IgE binding capability of said naturally occurring allergen, each of said at least four mutations being is a substitution of one surface-exposed amino acid residue with another residue, which does not occur in the same position in the amino acid sequence of any known homologous protein within the taxonomic species from which said naturally occurring allergen originates, each of said at least four mutations being is spaced from each other by at least 15 A, and said mutant allergen comprising at least one circular surface region with a area of 800 A that comprises no mutation of claim 1;

wherein the **each of said at least four mutations is spaced from each other by between about 20 to 30 A** of claim 2;

wherein said **at least four mutations are spaced from each other by at least 25 A** of claim 66;

wherein said **at least four the primary mutations are spaced from each other by at least 30 A** of claim 67;

which comprises at least five mutations in total, which each reduces the specific IgE binding capability of the mutated allergen as compared to the IgE binding capability of said naturally occurring allergen, **each of said at least five mutations in total being a substitution of one surface- exposed amino acid residue with another residue, which does not occur in the same position in the amino acid sequence of any known homologous protein within the taxonomic species from which said naturally occurring allergen originates, and at least two of said at least five mutations in total being spaced within 15 A of each other** of claim 3;

which comprises at least 8 total mutations and **wherein each of said at least four mutations spaced from each other by at least 15 A is spaced within 15 A of 1 to 4 of said at least 8 total mutations** of claim 15;

wherein at least one of the surface-exposed amino acids to be substituted in the naturally occurring allergen has a solvent accessibility of above 20 % of claim 4;

wherein at least one of the surface-exposed amino acids to be substituted in the naturally occurring allergen has a solvent accessibility of above 30 % of claim 68;

wherein at least one of the surface-exposed amino acids to be substituted in the naturally occurring allergen has a solvent accessibility of above 40 % of claim 69;

wherein at least one of the surface-exposed amino acids to be substituted in the naturally occurring allergen has a solvent accessibility of above 50 % of claim 70

wherein at least one of the surface-exposed amino acids to be substituted in the naturally occurring allergen is conserved with more than 70 % identity in all known homologous proteins within the species from which said naturally occurring allergen originates of claim 5;

wherein at least one of the surface-exposed amino acids to be substituted in the naturally occurring allergen is conserved with more than 80 % identity in all known homologous proteins within the species from which said naturally occurring allergen originates of claim 71;

wherein at least one of the surface-exposed amino acids to be substituted in the naturally occurring allergen is conserved with more than 90 % identity in all known homologous proteins within the species from which said naturally occurring allergen originates of claim 72

which essentially has the same (x-carbon backbone tertiary structure as said naturally occurring allergen of claim 6;

characterized in that when comparing the. (x-carbon backbone tertiary structures of the mutant and the naturally occurring allergen molecules, the average root mean square deviation of the atomic coordinates is below 2A of claim 9;

wherein each amino acid residue to be incorporated into the mutant allergen does not occur in the same position in the amino acid sequence of any known homologous

protein within the taxonomic genus from which said naturally occurring allergen originates of claim 7;

wherein each amino acid residue to be incorporated into the mutant allergen does not occur in the same position in the amino acid sequence of any known homologous protein within the taxonomic subfamily from which said naturally occurring allergen originates of claim 73;

wherein each amino acid residue to be incorporated into the mutant allergen does not occur in the same position in the amino acid sequence of any known homologous protein within the taxonomic family from which said naturally occurring allergen originates of claim 74;

wherein each amino acid residue to be incorporated into the mutant allergen does not occur in the same position in the amino acid sequence of any known homologous protein within the taxonomic superfamily from which said naturally occurring allergen originates of claim 75;

wherein each amino acid residue to be incorporated into the mutant allergen does not occur in the same position in the amino acid sequence of any known homologous protein within the taxonomic legion from which said naturally occurring allergen originates of claim 76;

wherein each amino acid residue to be incorporated into the mutant allergen does not occur in the same position in the amino acid sequence of any known homologous protein within the taxonomic suborder from which said naturally occurring allergen originates of claim 77;

wherein each amino acid residue to be incorporated into the mutant allergen does not occur in the same position in the amino acid sequence of any known homologous protein within the taxonomic order from which said naturally occurring allergen originates of claim 78;

characterized in that the specific IgE binding to the mutated allergen is reduced by at least 5% of claim 8;

characterized in that the specific IgE binding to the mutated allergen is reduced by at least 10% of claim 79;

characterized in said circular surface region comprises atoms of 15-25 amino acid residues of claim 10;

characterized in that the surface-exposed amino acid residues are ranked with respect to solvent accessibility, and that one or more amino acids among the more solvent accessible ones are substituted of claim 11;

characterized in that the surface-exposed amino acid residues are ranked with respect to degree of conservation in all known homologous proteins within the species from which said naturally occurring allergen originates, and that one or more amino acids among the more conserved ones are substituted of claim 12;

wherein the mutant allergen is a non-naturally occurring allergen of claim 13;

comprising from 5 to 20 mutations that reduce the specific IgE binding capability of the mutated allergen as compared to the IgE binding capability of said naturally occurring allergen, **each of said 5 to 20 mutations being a substitution of one surface-exposed amino acid residue with another residue, which does not occur in the same position in the amino acid sequence of any known homologous protein within the taxonomic species from which said naturally occurring allergen originates, and each of said 5 to 20 mutations being spaced from each other by at least 15 A** of claim 14;

comprising from 6 to 15 mutations that reduce the specific IgE binding capability of the mutated allergen as compared to the IgE binding capability of the said naturally occurring allergen, **each of said 6 to 15 mutations being a substitution of one surface-exposed amino acid residue with another residue, which does not occur in the same position in the amino acid sequence of any known homologous protein within the taxonomic species from which said naturally occurring allergen originates, and each of said 6 to 15 mutations being spaced from each other by at least 15 A** of claim 80;

comprising from 7 to 12 mutations that reduce the specific IgE binding capability of the mutated allergen as compared to the IgE binding capability of the said naturally occurring allergen, **each of said 7 to 12**

mutations being a substitution of one surface-exposed amino acid residue with another residue, which does not occur in the same position in the amino acid sequence of any known homologous protein within the taxonomic species from which said naturally occurring allergen originates, and each of said 7 to 12 mutations being spaced from each other by at least 15 A of claim 81;

comprising from 8 to 10 primary mutations that reduce the specific IgE binding capability of the mutated allergen as compared to the IgE binding capability of the said naturally occurring allergen, **each of said at said 8 to 10 mutations being a substitution of one surface-exposed amino acid residue with another residue, which does not occur in the same position in the amino acid sequence of any known homologous protein within the taxonomic species from which said naturally occurring allergen originates, and each of said 8 to 10 mutations being spaced from each other by at least 15A** of claim 82;

wherein said naturally occurring allergen is a house dust mite group 2 allergen selected from the group consisting of Der p 2, Der f 2 and Lep d 2 of claim 17;

a pharmaceutical composition comprising the recombinant mutant allergen according to claim 1 and at least one of a pharmaceutically acceptable carrier, excipient, or adjuvant of claim 35;

a composition comprising two or more recombinant mutant allergens **wherein each of said two or more recombinant mutant allergens respectively comprises at least one mutation among said at least four mutations spaced at least 15 A from each other that is absent in at least one other of said two or more recombinant mutant allergens** of claim 37;

further comprising at least one of a pharmaceutically acceptable carrier, excipient, or adjuvant of claim 39

a composition according to claim 37 comprising 2-12 recombinant mutant allergens of claim 38;

comprising 3-10 recombinant mutant allergens of claim 83; comprising 4-8 recombinant mutant allergens of claim 84;

comprising 5-7 recombinant mutant allergens of claim 85; and

comprising at least one T cell epitope capable of stimulating a T cell clone or T cell line specific for the naturally occurring allergen of claim 64.

Applicant's arguments filed on 11/04/2011 have been fully considered, but are not found persuasive.

Applicant argues:

"Claims 1-15, 17, 35, 37-39 and 66-85 remain rejected for alleged failure to comply with the written description requirement. The Examiner maintains the specification fails to provide adequate written description for the functional limitations set out in the claims and fails to adequately describe compositions comprising a plurality of recombinant mutant allergens or pharmaceutical compositions comprising recombinant mutant allergens. The rejection is respectfully traversed. Applicants' previously-filed amendments and responses have outlined in detail the reasons why the specification provides written description for the claimed invention. *See,* e.g., responses filed October 31, 2007, April 7, 2009 and August 4, 2010.

The rejected claims are directed to recombinant mutant allergens of a naturally occurring allergen selected from the group consisting of Fagales group 1 allergens, Vespidae antigen 5 allergens, house dust mite group 1 allergens, house dust mite group 2 allergens and grass group 5 allergens. *See* claim 1. The claims are thus directed to recombinant mutant allergens derived from Fagales group 1 allergens, Vespidae antigen 5 allergens, house dust mite group 1 allergens, house dust mite group 2 allergens and grass group 5 allergens and comprising at least four mutations, which each reduce the specific IgE binding capability of the mutated allergen as compared to the IgE binding capability of the naturally occurring allergen, each of said at least four mutations being a substitution of one surface-exposed amino acid residue with another residue, which does not occur in the same position in the amino acid sequence of any known homologous protein within the taxonomic species from which said naturally occurring allergen originates, each of said at least four mutations being spaced from each other by at least 15 A, and comprising at least one circular surface region with a area of 800 A^2 that comprises no mutation.

The specification provides adequate written description for the claimed recombinant mutant allergens. The written description requirement requires that the specification provide disclosure that allows one of ordinary skill in the art of the invention to "recognize that [the inventor] invented what is claimed." *Lockwood v. American Airlines, Inc.,* 107 F.3d 1565, 1572 (Fed. Cir. 1997); *see also Vas-Cath Inc. v. Mahurkar,* 935 F.2d 1555, 1563- 64 (Fed. Cir. 1991) (Applicant "must convey with reasonable clarity to those skilled in the art that ... he or she was in possession *of the invention.")* (emphasis in original). The written description requirement "ensure[s] that the scope of the right to exclude, as set forth in the claims, does not overreach the scope of the inventor's contribution to the field of art as detailed in the patent specification." *Reiff~n v. Microsoft Corp.,* 214 F.3d 1342, 1354 (Fed. Cir. 2000). The written description requirement is met by providing sufficient structural, physical and/or functional properties that describe a genus and/or a sufficient members of genus that show the inventors were in possession of the claimed invention. *Regents" of the University of California v. Eli Lilly & Co.,* 119 F.3d 1559, 1567-68 (Fed. Cir. 1997). Functional language may provide adequate written description "if in the knowledge of the art the disclosed function is sufficiently correlated with a particular, known structure." *Amgen Inc. v. Hoechst Marion Roussel, Inc.,* 314 F.3d 1313, 1332 (Fed. Cir. 2003) *citingEnzo Biochem, Inc. v. Gen-Probe, Inc.,* 296 F.3d 1316, 1324 (Fed. Cir. 2002).

The instant application sets forth the claimed invention in sufficient detail to show that Applicants were in possession of the claimed invention. Hence, the specification discloses that "the invention is based

on the recognition that a mutated allergen having IgE binding reducing mutations in multiple be cell epitopes, and at least one intact epitope" would reduce crosslinking IgE, and thus the allergenicity of the mutant allergens, while preserving at least one epitope to raise an IgG response. Specification at page 18, lines 29-36. The specification discloses that the recombinant mutant allergens are produced by making substitutions of at least four surfaced-exposed, conserved amino acids that are spaced from each other by at least 15 A, while preserving at least one circular surface region of 800 $A^{2.}$ Specification at, e.g., page 19, line 21-page 20, line 1. The spacing of the at least four mutations ensures that they are in separate clusters of epitopes. Specification at page 20, lines 14-17. In addition to the at least four mutations spaced at least 15 A from each other, the recombinant mutant allergens may further comprise additional mutations ("secondary mutations") that further reduce IgE binding. Specification at page 24, line 27 through page 25, line 8. These additional mutations are also placed such that a 800 A^2 area free of mutations is preserved. Specification at page 25, lines 2-3. The specification further sets forth detailed "Criteria for substitution." Specification at page 36-38.

The specification further gives detailed analysis on the structural features of Bet v 1, Der p 2, Ves v 5, Der p 1, and Phl p 5 and related proteins that further show possession of the claimed invention. Thus, the specification discloses 57 amino acids of Bet v 1 that are highly solvent exposed and conserved (page 68), 54 amino acids of Der p 2 that are highly solvent exposed and conserved (page 72), 88 amino acids ofVes v 5 that are highly solvent exposed and conserved (page 76) and sets forth 12 Der p 2 mutants (pages 97-98), 11 Der p 1 mutants (pages 105-106), 14 Phi p 5 mutants (pages 114-115). The detailed description of amino acids to be mutated and the combinations of mutants demonstrate that the inventors had possession of the claimed invention as it relates to Bet v 1, Ves v 5, Der p 1, Der p 2, and Phl p 5. Moreover, as disclosed in the specification, Bet v 1, Ves v 5, Der p 1, Der p 2, and Phi p 5 are highly homologous to allergens Fagales group 1 allergens, Vespidae antigen 5 allergens, house dust mite group 1 allergens, house dust mite group 2 allergens and grass group 5 allergens, respectively. See specification at page 81, lines 1-15 (67 sequences homologous to Bet v 1 within the order Fagales), page 58 and Fig. 10 A (Vespula Ag 5s about 90% identical), Fig. 35 A and B (sequence alignment of Der p 1 and other house dust mite group 1 allergens), Fig. 32 (sequence of Der p 2 with other house dust mite group 2 allergens), and Fig. 38 A-D (sequence alignment of Phi p 5 with other grass group 5 allergens). One of ordinary skill in the art would understand that the high degree of sequence identity among the members of the respective allergen families recited in the claims means that description of recombinant mutant allergens for a single member of the family provides written description for recombinant mutant allergens of any allergen within the same family. Thus, the specification provides written description for the recombinant mutant allergens called for in the subsisting claims.

In setting forth the instant rejection, the Examiner has cited *Eli Lilly, supra.* The nature of the instant invention and the disclosure of the instant specification, however, are very different from *Eli Lilly.* In *Eli Lilly,* the Federal Circuit held that the disclosure of the sequence of a rat insulin cDNA did not provide adequate written description for the insulin cDNA sequence of every vertebrate. *Eli Lilly* at 1566-67. In *Eli Lilly,* however, the specification failed to provide any features that described the claimed vertebrate insulin cDNA. The Court found that the claimed cDNA were described solely by their function or how to obtain them. The instant case is inapposite to *Eli Lilly.* In *Eli Lilly* the claims were directed to unknown cDNA sequences. The instant claims, by contrast, are drawn to mutant allergens that are derived by making substitutions in a family of allergens, i.e., Fagales group 1 allergens, Vespidae antigen 5 allergens, house dust mite group 1 allergens, house dust mite group 2 allergens and grass group 5 allergens, with closely related sequences. In *Eli Lilly,* no structural features were provided that correlated with the function of the claimed vertebrate insulin cDNA. In the instant case, the specification provides that substituted amino acids are those amino acids that are conserved, solvent accessible amino acids that are spaced at least 15 A from each other and which are each outside a circular area of 800 A^2 on the surface of the allergen and goes on to list particular
amino acids to choose among to make the claimed recombinant mutant allergens.

Nor does the decision of the Board of Patent Appeals and Interferences in *ex parte Kubin* (83 USPQ2d 1410 (BPAI 20071)) support a finding that the instant specification fails to provide adequate written description for the pending claims. In *Kubin,* the Board upheld the rejection of a claim directed to isolated polynucleotides encoding polypeptides that (1) "are at least 80% identical to amino acids 22-221 of SEQ ID NO: 2" (i.e., the amino acid sequence for the extracellular domain of the protein natural killer cell activation inducing ligand ("NAIL") lacking the NAIL signal sequence) and (2) which bind to the glycoprotein CD 48. *Id.* at 1417. The specification in *Kubin* disclosed the sequence of two nucleic acids within the scope of the claim and three fusion proteins whose nucleic acid sequences would fall within the scope of the claim. *Id.* None of these sequences varied amino acids 22-221 of SEQ ID NO: 2. *Id.*

The Board in *Kubin* found that the Applicant had failed to describe what domains of within amino acids 22-221 of SEQ ID NO: 2 correlated with the function of binding CD 48, and thus the Applicant had not described which NAIL amino acids could be varied and still maintain CD 48 binding. *Id.* Citing *Eli Lilly,* the Board found that in the absence of a structure- function correlation, the claim merely defined the invention by function, which was not sufficient to satisfy the written description requirement.

Kubin is distinguished from the instant case for much the same reasons as *Eli Lilly.* In *Kubin,* the Applicant failed to provide any features of amino acids 22-221 of SEQ ID NO: 2 that correlated with binding to CD 48. As set forth above, the instant specification, in contrast, allows one of ordinary skill in the art to identify amino acids Fagales group 1 allergens, Vespidae antigen 5 allergens, house dust mite group 1 allergens, house dust mite group 2 allergens and grass group 5 allergens. Furthermore, whereas in *Kubin* the Applicant failed to disclose any polynucleotides encoding NAIL protein that varied in amino acids 22-221, the instant applications identifies numerous amino acid for substitution in Fagales group 1 allergens, Vespidae antigen 5 allergens, house dust mite group 1 allergens, house dust mite group 2 allergens and grass group 5 allergens, and further sets forth examples of combinations of mutants, whereas the Applicant in *Kubin* failed to provide any working examples of polynucleotides encoding a polypeptide at least 80% identical to amino acids 22-221 of SEQ ID NO: 2 and which bind CD 48.

In short, as with *Eli Lilly,* the Applicant in *Kubin* failed to provide any structural features that correlated with the function of the polypeptide called for in the claim, whereas the instant specification sets out the features, including specific amino acids, of Fagales group 1 allergens, Vespidae antigen 5 allergens, house dust mite group 1 allergens, house dust mite group 2 allergens and grass group 5 allergens that are called for in the claims and which allow one of ordinary skill in the mutant art to make the claimed recombinant allergens. Thus, the basis of the Board's decision in *Kubin* does not apply to the instant claims.

The structure of Bet v 1 was known at the time the application was filed and Bet v 1 allergens are highly conserved. There is no rule that the Applicants provide description of the precise mutant amino acids in the claimed recombinant Bet v 1 mutants. *Falkner v. Inglis,* 448 F.3d 1357, 1366 (Fed. Cir. 2006). Applicants are entitled to "flexibility" in how they claim their invention. *Univ. of Rochester v. G.D. Searle & Co., Inc.,* 358 F.3d 916, 927-928 (Fed. Cir. 2004). In *Ariad v. Eli Lilly,* the Federal Circuit reiterated, "[written description] doctrine never created a heightened requirement to provide a nucleotide-by-nucleotide recitation of the entire genus of claimed genetic material; it has always expressly permitted the disclosure of structural features common to the members of the genus." *Ariad Pharmaceuticals', Inc. v. Eli Lilly and Co.,* cv 2008-1248, Fed. Cir., *en banc,* decided March 22, 2010, slip op at 26, *citations omitted.* Here, when measured against the known, conserved structure of Bet v 1 allergens and the high level of skill in the art concerning B-cell epitopes, the claims tell one of ordinary skill in the art where mutations are placed in the claimed recombinant allergens. The claims thus describe the claimed invention and do not "merely [draw] a fence around the outer limits of a purported genus." *Id.* at 21.

In short, the specification teaches that the starting point for the claimed recombinant mutant allergens are known proteins, i.e., a naturally occurring allergens, and further gives clear teachings on how to use such starting material to arrive at the claimed invention. The state of the art, moreover, is high. One of ordinary skill in the art would thus immediately envision that the claimed recombinant mutant allergens bearing the mutations made according the teachings of the specification would largely retain the structure

and antigenicity of wild-type allergens from which they are derived. The Examiner has failed to adduce any evidence to the contrary.

Additionally, the Examiner's statements t "Applicants have no way of knowing how to modify as yet undiscovered allergens that may differ from known allergens in ways that cannot be contemplated" and there "is no way to know what is or is not an allergen encompassed by the scope of the claims given the information disclosed in the specification" are not well taken. First the possibility that, notwithstanding the conserved structure of antigenicity among allergens in the same family, "undiscovered allergens that may differ from known allergens in ways that cannot be contemplated" is pure conjecture on the basis of the Examiner is therefore of little probative value. Contrary to the Examiner's assertion, the specification teaches precisely how to modify as yet undiscovered naturally-occurring allergens to arrive at the claimed invention. Lastly, the Examiner's statements concerning the scope of the claims blur the requirements for indefiniteness, enablement, and written description. These are additional reasons why the written description rejection should be withdrawn.

Lastly, the Examiner's comments concerning the difference among the allergens disclosed in Smith are not well taken. As set forth above, "naturally-occurring" allergens are not encompassed by the claims. Thus, Smith does not provide evidence that the specification fails to provide written description for the claimed invention.

For at least the reasons set forth above, the specification provides sufficient written description to show Applicants were in possession of the full scope of the claimed invention when the application was filed. Reconsideration of the claims and withdrawal of all rejections thereof for lack of written description is requested.

For at least the reasons set forth above, the specification provides sufficient written description to show Applicants were in possession of the full scope of the claimed invention when the application was filed. Reconsideration of the claims and withdrawal of all rejections thereof for lack of written description is requested."

Applicant's assertion that the undiscovered allergens may differ from known allergens in ways that cannot be contemplated “is pure conjecture and of little probative value” is not well taken. In support of this contention, the Examiner has provided the Radauer et al. reference entitled: ‘The Bet v 1 fold: an ancient, versatile scaffold for binding of large, hydrophobic ligands’ (PTO-892; Reference U). The reference teaches that plants are continuously challenged by pathogens, herbivores and adverse environmental conditions and have evolved numerous other mechanisms of stress response and defense including pathogen-specific resistance genes and inducible pathogenesis-related (PR) proteins. An unusual PR family was designated PR-10 which in contrast to most PR families, is expressed in the cytoplasm. The major pollen allergen

of white birch (*Betula verrucosa*), Bet v 1, was cloned and its sequence revealed to be similar to PR-10 proteins. Homologous allergens from pollen of related trees such as alder and hazel as well as food allergens from fruits and vegetables such as apple and celery were identified. Immunoglobulin E cross-reactivity among these allergens is responsible for the frequent occurrence of plant food allergy among birch pollen allergic individuals.

A comparison of the structures, functions and taxonomic distributions of members of the Bet v 1-like superfamily leads to the suggestion that a protein possessing the Bet v 1 fold most likely already existed in the last universal common ancestor. The biological function of this protein was probably related to lipid binding and the primordial gene subsequently diverged into the multitude of Bet v 1-related protein families present today, some of which retained the original fold, while others gained novel function by insertion of additional structural elements. Functional diversity within the Bet v 1-like superfamily was
also accomplished by fusion to other domains such as DNA binding modules of transcription regulators found as members of several Bet v 1-related families. During evolution, sequence similarity between members of different families decreased to values that make the prediction of homology unreliable. However, it is unlikely that this fold with the distinctive topology of an anti-parallel beta-sheet wrapped around a long alpha-helix forming a large cavity. Bet v 1 from birch pollen and its close homologues from other Fagales tree pollen are the only proteins within this ubiquitously distributed superfamily known to be capable of initiating an allergic immune response in humans. The comparison of Bet v 1 with its non-allergenic structural homologues offers the possibility to shed light on such features.

The reference teaches that structural comparisons of representative members of already known protein families structurally related to Bet v 1 with all entries of the Protein Data Bank yielded 47 structures with non-identical sequences. They were classified into eleven families, five of which were newly identified and not included in the Structural Classification of Proteins database release 1.71. Comparison of ligand binding activities of Bet v 1-like superfamily members revealed that their functions were related to binding and metabolism of large, hydrophobic compounds such as lipids, hormones, and antibiotics. Phylogenetic relationships within the Bet v 1 family, defined as the group of proteins with significant sequence similarity to Bet v 1, were determined by aligning **264 Bet v 1-related sequences**. A distance-based phylogenetic tree yielded a classification into 11 subfamilies, nine exclusively containing plant sequences and two subfamilies of bacterial proteins. Plant sequences included the pathogenesis-related proteins 10, the major latex proteins/ripening-related proteins subfamily, and polyketide cyclase-like sequences. The ubiquitous distribution of Bet v 1-related proteins among all superkingdoms suggests that a Bet v 1-like protein was already present in the last universal common ancestor. During evolution, this protein diversified into numerous families with low sequence similarity but with a common fold that succeeded as a versatile scaffold for binding of bulky ligands.

Therefore, it is without question that Bet v1 has changed over time and will continue to change over time and that what is encompassed by the term "naturally occurring Bet v 1 allergen from the order Fagales" is not in Applicant's possession, particularly given the fact that Bet v1 is a pathogenesis-related (PR) proteins whose purpose is to protect the plant from pathogen

challenge. The Bet v 1 allergen has changed and will change again in ways that are not predictable.

Furthermore, the state of skill in the art is high, but that does not change the fact that one of ordinary skill in the art would not be able to determine what is encompassed by the instant claim recitations. The written description requirement is separate from the enablement requirement, which the Examiner agrees is fulfilled by the disclosure in the specification. One could make and use the invention commensurate in scope with the claims without performing undue or excessive experimentation. However, the specification does not adequately describe the genus of allergens that are encompassed by the instant claim recitations.

The written description requirement is to adequately identify what one has been invented to prevent an applicant for patent from perpetrating a fraud on the public and later claiming exclusive rights to that what he or she did not in fact invent. Furthermore, the requirement for an adequate disclosure ensures that the public receives something in return for the exclusionary rights that are granted to the inventor by a patent because upon the grant of a patent in the U.S., the information contained in the patent becomes a part of the information available to the public for further research and development, subject only to the patentee's right to exclude others during the life of the patent. The patentee must disclose in the patent sufficient information to put the public in possession of the invention and to enable those skilled in the art to make and use the invention. Therefore, the sufficiency of written description requirement is important for those of ordinary skill in the art to know what is being claimed so as not to infringe the patented claims and after the patent expires to be able to know what is then in the public realm.

As such, the specification must describe a correlation between the amino acid structure of the genus of all of the mutant allergens encompassed and the function of exhibiting reduced IgE binding such that a skilled artisan would have known what modifications to make the Fagales group 1 allergens, Vespidae antigen 5 allergens, house dust mite group 1 allergens, house dust mite group 2 allergens and grass group 5 allergens to attain the claimed function and functional limitations.

"Possession may not be shown by merely describing how to obtain possession of member of the claimed genus or how to identify their common structural features" In re Kubin, of record, at page 16. "Without a correlation between structure and function, the claim does little more than define the claimed invention by function" *supra*, at page 17.

Applicant argues that the instant applications identifies numerous amino acid for substitution in Fagales group 1 allergens, Vespidae antigen 5 allergens, house dust mite group 1 allergens, house dust mite group 2 allergens and grass group 5 allergens, and further sets forth examples of combinations of mutants. However, given that Applicant is not in possession of the genus of allergens to be modified, Applicant is accordingly not in possession of the genus of mutants that can be made to a genus of allergens that they do not and cannot possess. Applicants have no way of knowing how to modify as yet undiscovered allergens that may differ from known allergens in ways that cannot be contemplated.

The limitation of being a 'mutant allergen of a naturally occurring allergen' is not adequately described because it is impossible to distinguish between a mutant and a naturally

occurring sequence until such a naturally occurring sequence becomes part of the art in the field. The scope would be changeable as more wild-type allergen sequences are identified.

Applicant argues that the instant specification sets out the features, including specific amino acids, of Fagales group 1 allergens, Vespidae antigen 5 allergens, house dust mite group 1 allergens, house dust mite group 2 allergens and grass group 5 allergens that are called for in the claims and which allow one of ordinary skill in the mutant art to make the claimed recombinant allergens. What one of ordinary skill in the art could do with time and experimentation is not at issue here. What is at issue here is whether Applicant is in possession of their claimed invention. There is no way to know what is or is not an allergen that is encompassed by the scope of the claims given the information disclosed in the specification. The specification has not adequately disclosed a correlation between the amino acid structure of the genus of all of the mutant allergens encompassed and the function of exhibiting reduced IgE binding. There is no way to know what is encompassed by the term " a mutant naturally occurring allergen" and whether a particular residue does not occur in the same position in a homologous allergen. If one were to later discover a homologous allergen with a previously undiscovered amino acid in a previously undiscovered isoform of one of the recited allergens in one of the recited positions would that naturally occurring sequence be a mutant of a naturally occurring sequence? One of ordinary skill in the art would not be able to determine what is encompassed by the instantly recited recombinant mutant allergen of a naturally occurring allergen.

The art of Smith et al. (PTO-892 mailed on 10/06/2010; Reference U) aligns the sequences of Der p 2, Eur m2, Lep d 2 and Typ d 2, all homologous, recited Group 2 mite

allergens. You can see in Figure 1 where the sequences differ from one another. It is easy to see that mutations specifically listed in the specification on pages 31-32 specifically list "mutations" that are present naturally in other allergens. See, for example, K15E and K48A which the specification lists as an acceptable mutation for the claimed invention. Those are naturally occurring positions in Lep d 2. Therefore, those amino acids substitutions are not those "which does not occur in the same position in the amino acid sequence of any known homologous protein within the taxonomic species." Applicant's argument that those sequences in Figure 1 are somehow not naturally occurring is not persuasive.

It remains the Examiner's position that the specification does not adequately disclose a correlation between the structure of the claimed recombinant allergens (complete combinations of specific mutations to a reference sequence) and function (which each reduce the specific IgE binding capability of the mutated allergen as compared to the IgE binding capability of said naturally occurring allergen) such that a skilled artisan would have known what modifications to make to the allergens to attain the claimed function and functional limitations.

Applicant has disclosed only the specific recombinant mutants of Ves v 5, Bet v 1, Der p 2, Der p 1 and Phl p 5 in Examples 1-10 in the specification; therefore, the skilled artisan cannot envision all the contemplated recombinant allergen mutant possibilities recited in the instant claims.

The rejection is maintained.

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nora M. Rooney whose telephone number is (571) 272-9937. The examiner can normally be reached Monday through Friday from 8:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

February 3, 2012
/Nora M Rooney/
Primary Examiner, Art Unit 1644